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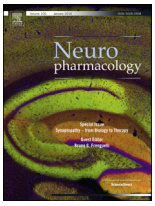

Invited review

IRSp53/BAIAP2 in dendritic spine development, NMDA receptor regulation, and psychiatric disorders

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ABSTRACT

IRSp53 (also known as BAIAP2) is a multi-domain scaffolding and adaptor protein that has been implicated in the regulation of membrane and actin dynamics at subcellular structures, including filopodia and lamellipodia. Accumulating evidence indicates that IRSp53 is an abundant component of the postsynaptic density at excitatory synapses and an important regulator of actin-rich dendritic spines. In addition, IRSp53 has been implicated in diverse psychiatric disorders, including autism spectrum disorders, schizophrenia, and attention deficit/hyperactivity disorder. Mice lacking IRSp53 display enhanced NMDA (N-methyl-D-aspartate) receptor function accompanied by social and cognitive deficits, which are reversed by pharmacological suppression of NMDA receptor function. These results suggest the hypothesis that defective actin/membrane modulation in IRSp53-deficient dendritic spines may lead to social and cognitive deficits through NMDA receptor dysfunction.

This article is part of the Special Issue entitled 'Synaptopathy – from Biology to Therapy'.

1. Introduction

IRSp53 (for insulin receptor substrate p53), also known as BAIAP2 (brain-specific angiogenesis inhibitor 1-associated protein 2), is a multi-domain adaptor protein originally identified as a protein that is tyrosine phosphorylated by the insulin receptor and IGF-1 (insulin-like growth factor 1) receptor (Yeh et al., 1996). Subsequent studies have firmly established IRSp53 as an important regulator of membrane and actin dynamics at actin-rich subcellular structures, including filopodia and lamellipodia (Ahmed et al., 2010; Scita et al., 2008; Suetsugu et al., 2010).

Although the functions of IRSp53 have been mainly studied in non-neural cells, steadily accumulating evidence supports neuronal functions of IRSp53, in particular, in the regulation of membrane/actin dynamics at excitatory synapses and dendritic spines. The first such evidence was a report that identified IRSp53 as an important component of the postsynaptic density (PSD) (Abbott et al., 1999)—multi-protein complexes in the postsynaptic side of excitatory synapses that couple receptor activation with downstream signaling (Emes and Grant, 2012; Kennedy, 1993; Sheng and Hoogenraad, 2007; Sheng and Kim, 2011).

More recently, IRSp53/BAIAP2 has been implicated in several psychiatric disorders, including autism spectrum disorders (ASDs) (Celestino-Soper et al., 2011; Levy et al., 2011; Toma et al., 2011), schizophrenia (Fromer et al., 2014; Purcell et al., 2014), and attention deficit/hyperactivity disorder (ADHD) (Liu et al., 2013; Ribases et al., 2009). In parallel, neurobiological studies on mice lacking IRSp53 (*IRSp53*$^{-/-}$ mice) have revealed that IRSp53 deletion leads to synaptic and behavioral abnormalities that are reminiscent of symptoms of IRSp53-related psychiatric disorders, suggesting the possibility of IRSp53-related synaptopathies.

In this review, we will summarize the reported roles of IRSp53 in the regulation of membrane/actin dynamics, dendritic spine development, NMDA receptor (NMDAR) function, and social and cognitive behaviors. In addition, we will discuss how the deletion of the IRSp53 gene leads to enhanced NMDA (N-methyl-D-aspartate) receptor (NMDAR) function, which is associated with social and cognitive deficits in *IRSp53*$^{-/-}$ mice.

2. Domain structure of IRSp53

The IRSp53 gene is located at human chromosome 17q25 and mouse chromosome 11E2. These genes are predicted to consist of

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17 and 16 exons, respectively (Miyahara et al., 2003).

The IRSp53 protein contains multiple domains for protein–-protein interactions, including an IMD (IRSp53-MIM homology domain; also known as an I-BAR) domain, a CRIB-PR (Cdc42/Rac interactive binding-proline rich) domain, an SH3 (Src homology 3) domain, a WW domain, a WH2 (WASP homology 2) domain, and a C-terminal PDZ-B (PSD-95/Dlg/ZO-1 domain-binding) motif (Fig. 1A). The IMD/I-BAR domain is known to bind to and deform the plasma membrane, creating a negative membrane curvature (Suetsugu et al., 2010).

IRSp53 shares a similar domain structure, with the exception of the CRIB-PR domain (Yamagishi et al., 2004), with two other members of the IRSp53 subfamily of IMD-containing proteins: IRTKS (insulin receptor tyrosine kinase substrate; also known as BAIAP2L1), which is minimally expressed in the brain (Millard et al., 2007), and FLJ22582 (BAIAP2L2), which has been minimally studied (Yamagishi et al., 2004). Drosophila and *Caenorhabditis elegans* also have proteins with a similar domain structure (Yamagishi et al., 2004).

Alternative splicing generates a total of five splice variants of IRSp53, four in humans and three in mice, four of which—S, L, M, and T forms—mainly differ in the C-terminal region, sharing the first 511 aa residues, whereas the fifth, termed the B form here (IRSp53-B), lacks ~40 aa in the CRIB-PR domain (Alvarez and

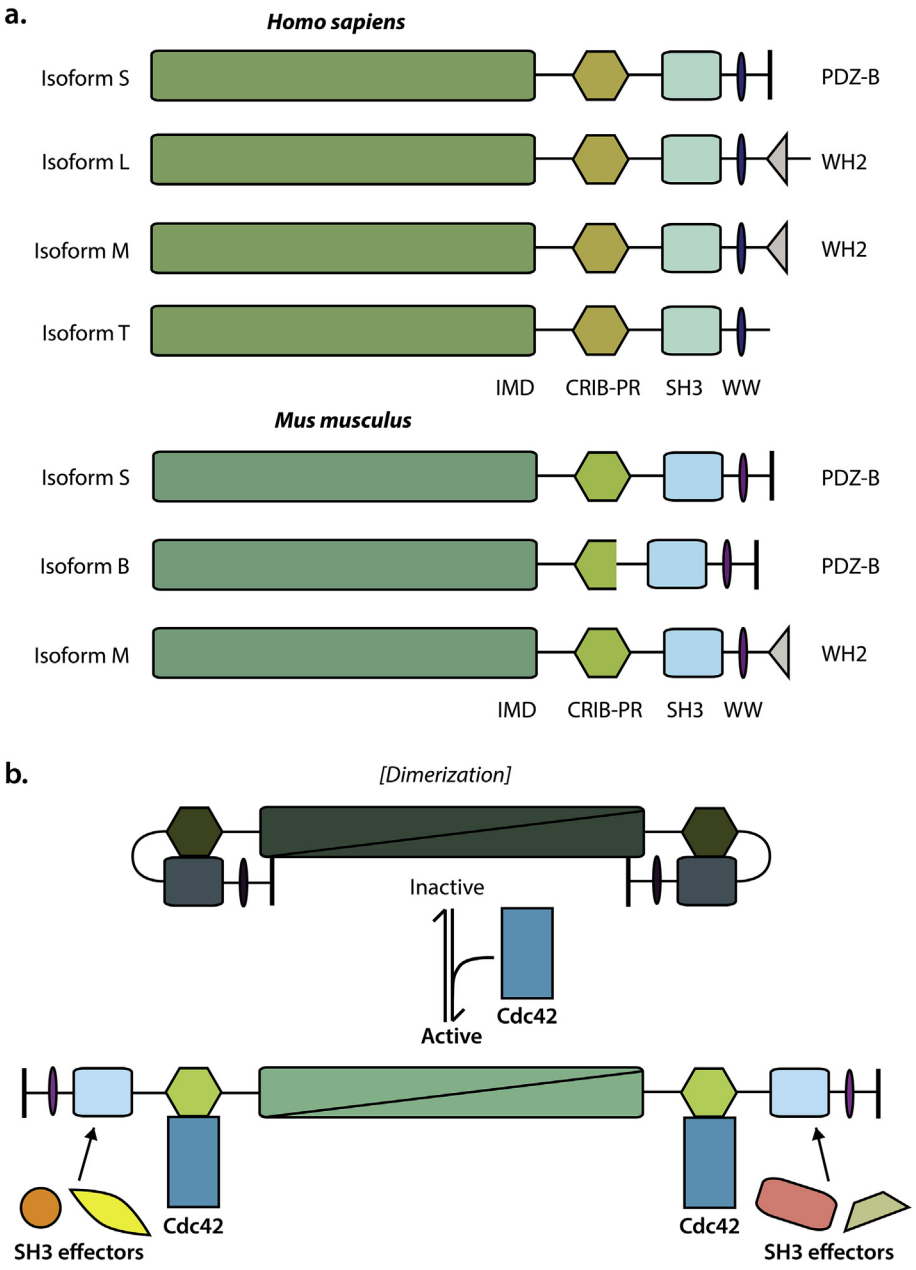

Fig. 1. Domain structure, splice variants, and activation mechanisms of IRSp53. (A) Domain structure and splice variants identified in humans and mice. Note that the splice variations are mainly observed in C-terminal regions, except for the B form in mice lacking a part of the CRIB-PR domain. IMD, IRSp53-MIM homology domain; CRIB-PR, Cdc42/Rac interactive binding-proline rich domain; SH3, Src homology 3 domain; WW, WW domain; PDZ-B, PSD-95/Dlg/ZO-1 domain-binding motif; WH2, WASP homology 2 domain. (B) Autoinhibition and activation mechanisms in IRSp53. Head-to-head dimers of IRSp53 are autoinhibited in a closed conformation through an intramolecular interaction involving the CRIB-PR and SH3 domains. Binding of activated (GTP-bound) Cdc42 to the CRIB-PR domain opens up the protein, allowing the SH3 domain to bind downstream effectors such as N-WASP and WAVE2.

Williams, 1998; Govind et al., 2001; Miyahara et al., 2003; Oda et al., 1999; Okamura-Oho et al., 1999). These variants could be functionally distinct because the S and L forms are phosphorylated by insulin stimulation, whereas the T form is phosphorylated by IGF-1 stimulation (Okamura-Oho et al., 2001).

There are two major IRSp53 protein species in rodent brains with apparent molecular masses of ~58 and 53 kDa. The molecular nature of these proteins is unclear, although they likely represent the S from with or without the 40-aa splice insert in the CRIB-PR domain. In support of this possibility, immunoblotting and reverse transcription-polymerase chain reaction (RT-PCR) data indicate that the S variant is the main isoform expressed in rat cultured hippocampal neurons (Hori et al., 2005). Both IRSp53 species coimmunoprecipitate with the excitatory postsynaptic PDZ protein PSD-95 in rat brains (Choi et al., 2005; Soltau et al., 2004), suggesting that they both have the PDZ-B motif, which is present in the S form. In vitro protein translation of mouse S forms with or without the 40-aa insert yields protein species of ~58 and 53 kDa (Alvarez et al., 2002). Post-translational modification is unlikely to account for the two bands, because the 5 kDa difference between them is unlikely to be caused by protein phosphorylation, and deglycosylation enzymes have no effect on the protein band sizes (Abbott et al., 1999). Functionally, if the 58 and 53 kDa proteins differ in the CRIB-PR domain, they are likely to have distinct autoinhibitory mechanisms (see below for details).

3. Expression patterns of IRSp53 mRNAs and proteins

Northern blot analyses indicate that IRSp53 is expressed most strongly in the brain, but also in other tissues, including the spleen, lung, liver, and testis (Abbott et al., 1999; Bockmann et al., 2002). In the brain, IRSp53 mRNAs are detected in regions including the cortex, hippocampus, striatum, and cerebellum (Bockmann et al., 2002).

At the protein level, IRSp53 expression, measured by X-gal staining of *IRSp53*$^{+/-}$ mouse brain slices, is observed in regions including the cortex, hippocampus, striatum, and cerebellum (Kim et al., 2009a; Sawallisch et al., 2009), a distribution pattern similar to that of the corresponding mRNA. In addition, Immunohistochemical analyses with specific IRSp53 antibodies indicate a similar distribution pattern of endogenous IRSp53 proteins in rat brains (Bockmann et al., 2002; Burette et al., 2014).

4. Protein interactions of IRSp53

A role for IRSp53 in the regulation of membrane and actin dynamics is supported by the fact that IRSp53 interacts with membranes, actin filaments, small GTPases, actin regulatory proteins, and PDZ domain-containing scaffolding proteins. Many of these proteins regulate neuronal/synaptic functions, and some have been implicated in brain disorders (Table 1).

The N-terminal IMD domain binds and deforms PI(4,5)P_2- and PI(3,4,5)P_3-rich membranes through its I-BAR activity (Mattila et al., 2007; Suetsugu et al., 2006). In addition, the IMD domain of IRSp53 binds and bundles actin filaments (Yamagishi et al., 2004), although its role in membrane deformation is unclear (Safari and Suetsugu, 2012). Two IMD domains form an antiparallel dimer (Millard et al., 2005), leading to the dimerization of full-length IRSp53 proteins in a head-to-head manner (Fig. 1B). The CRIB-PR domain binds the GTP-bound (activated) form of the small GTPase Cdc42 (Govind et al., 2001; Krugmann et al., 2001). Because Cdc42 itself is tethered to the plasma membrane, both IMD and Cdc42 contribute to the membrane targeting of IRSp53, in line with the concept that phosphoinositides and small GTPases act in synergy to recruit cytoplasmic proteins to specific compartments of the plasma membrane (Di Paolo and De Camilli, 2006).

In the full-length IRSp53 protein, interaction of the SH3 domain with binding partners is thought to be inhibited through an intramolecular interaction involving the CRIB-PR and SH3 domains (Alvarez et al., 2002; Disanza et al., 2006; Kast et al., 2014). This autoinhibition of IRSp53 is relieved by Cdc42 binding to the CRIB-PR domain (Alvarez et al., 2002; Govind et al., 2001; Kast et al., 2014; Krugmann et al., 2001), allowing the SH3 domain to bind its effectors. Many of these effectors are actin modulatory proteins such as WAVE-2, N-WASP, Eps8, Ena/VASP, and mDia1, which in many cases converge onto the Arp2/3 complex (Table 1), known to promote nucleation of branched actin filament networks (Scita et al., 2008). The autoinhibition of IRSp53 also suppresses the interaction of the IMD domain with membranes, as supported by the limited localization of the autoinhibited protein in the plasma membrane (Kast et al., 2014).

In addition to regulating actin dynamics, the SH3 effectors of IRSp53 enhance additional opening/activation of IRSp53. For instance, dual binding of Cdc42 and SH3 effectors such as Eps8 (Funato et al., 2004), to IRSp53 synergistically induces full opening/activation of IRSp53 (Disanza et al., 2006; Kast et al., 2014). WAVE-2 binding to the SH3 domain enhances Rac1 binding to the IMD domain (Miki and Takenawa, 2002; Miki et al., 2000). In addition, some SH3 effectors such as Tiam1 (a guanine nucleotide exchange factor or GEF for Rac) and Eps8 (coupled to Sos-1 and Abi-1, both with Rac-GEF activities) activate Rac1 (Connolly et al., 2005; Funato et al., 2004), suggesting that IRSp53 can act both upstream and downstream of Rac. These mechanisms are thought to contribute to IRSp53-dependent formation of actin-rich protrusive structures such as filopodia (Govind et al., 2001; Krugmann et al., 2001; Yamagishi et al., 2004) and lamellipodia (Miki et al., 2000) at the interface of membranes and actin filaments.

The WH2 domain is generally known to bind monomeric actin, but the WH2 domain in IRSp53 is dissimilar to canonical WH2 domains, and thus its function is unclear (Scita et al., 2008). Lastly, the C-terminal PDZ-binding (PDZ-B) motif interacts with diverse PDZ domain-containing scaffolding proteins, including PSD-95, PSD-93/Chapsyn-110, and MALS/LIN-7 (Choi et al., 2005; Hori et al., 2003; Soltau et al., 2004).

5. Synaptic localization of IRSp53

Since the identification of IRSp53 as a core component of the PSD and excitatory synapses (Abbott et al., 1999), additional experimental evidence has supported the excitatory synaptic localization of IRSp53. For instance, in situ hybridization and immunoblot analyses of biochemical rat brain fractions indicate that IRSp53 expression is significantly increased during the first 3 weeks of postnatal brain development (Bockmann et al., 2002; Choi et al., 2005), during which active synaptogenesis occurs.

Ultrastructural electron microscopy (EM) indicates that IRSp53 proteins are present in the PSD as well as at other sub-regions of dendritic spines such as tangential walls and spine cytosolic regions (Choi et al., 2005). A more recent EM study reported that IRSp53 displays distinct distribution patterns within the PSD in different brain regions. In spiny excitatory neurons of the neocortex and hippocampus, IRSp53 is concentrated in the center of the PSD rather than in the periphery, whereas it is uniformly distributed along the lateral axis of the PSD in spiny inhibitory neurons of the neostriatum and cerebellar cortex (Burette et al., 2014). The reasons for these differences are unclear.

Synaptic localization of IRSp53 appears to be regulated by neuronal activity. NMDA receptor stimulation in cultured hippocampal neurons promotes synaptic localization of IRSp53 in a manner requiring protein kinase C activation, the IMD and PDZ-B

Table 1
Binding partners of IRSp53 and their neuronal/synaptic functions and associations with brain disorders.

Domain	Binding partner	Function of interaction	Partner's neuronal/synaptic function	Partner's association with brain disorders
IMD	F-actin (Yamagishi et al., 2004)	Actin bundling (Yamagishi et al., 2004)	Main cytoskeleton in dendritic spines	
	IRSp53 (Millard et al., 2005)	Forms IRSp53 dimers (Millard et al., 2005)	Actin and membrane dynamics in spines (Scita et al., 2008)	ASD, schizophrenia, and ADHD (See Table 3 for details)
	Kank1 (Roy et al., 2009)	Inhibits Rac1-IRSp53 interaction (Roy et al., 2009)	Suppresses actin filament formation (Kakinuma et al., 2008)	Cerebral palsy (Lerer et al., 2005) ASD, motor/cognitive dysfunctions (Vanzo et al., 2013)
	Rac1 (Miki et al., 2000)	Links Rac1 and Wave (Miki et al., 1998; Miki et al., 2000) Membrane deformation (Suetsugu et al., 2006)	Neuronal development (Govek et al., 2005; Tolias et al., 2011)	
CRIB-PR	Cdc42 (Govind et al., 2001; Krugmann et al., 2001)	Relieves autoinhibition (Krugmann et al., 2001)	Neuronal development (Govek et al., 2005; Tolias et al., 2011)	
Between CRIB-PR and SH3	14-3-3ζ (Robens et al., 2010)	Inhibits IRSp53 binding to SH3 effectors and Cdc42 (Robens et al., 2010)	Neural signaling, development, and protection (Foote and Zhou, 2012)	ASD (Toma et al., 2013)
SH3	BAI1 (Oda et al., 1999)	Localizes IRSp53 to membranes (Oda et al., 1999)	Synaptogenesis and spine formation (Stephenson et al., 2014)	
	BRAG1/IQ-ArfGEF (Sanda et al., 2009)	Regulate ARF signaling in dendritic spines (Sanda et al., 2009)	Synaptic plasticity (Myers et al., 2012)	Intellectual disability (Shoubridge et al., 2010)
	Cypin (Barilari and Dente, 2010)	Form the CIPP-Cypin-IRSp53 complex (Barilari and Dente, 2010)	Microtubules and dendrite patterning (Tseng and Firestein, 2011)	
	DRPLA/Atrophin-1 (Okamura-Oho et al., 1999)	May regulate insulin/IGF-1 signaling pathways (Okamura-Oho et al., 1999)	Transcriptional co-repressor (Shen and Peterson, 2009)	DRPLA (Tsuji, 2012)
	Dynamin1 (Chou et al., 2014)	Promotes filopodia formation (Chou et al., 2014)	Membrane fission during endocytosis (Ferguson and De Camilli, 2012)	Epilepsy (Ferguson and De Camilli, 2012)
	Eps8 (Funato et al., 2004)	Activates IMD-bound Rac (Funato et al., 2004)	Dendritic spines (Menna et al., 2013; Stamatakou et al., 2013)	ASD (Menna et al., 2013)
	Espin (Sekerkova et al., 2003)	Regulates actin binding and bundling (Sekerkova et al., 2003)	Stereociliary actin bundle (Sekerkova et al., 2011).	Deafness, vestibular dysfunction (Naz et al., 2004)
	mDia1 (Fujiwara et al., 2000)	Promotes filopodia formation (Goh et al., 2012)	Migration of interneuron precursors (Shinohara et al., 2012)	
	Mena (Krugmann et al., 2001)	Induces filopodia formation (Krugmann et al., 2001)	Neuronal polarity (Drees and Gertler, 2008; Neukirchen and Bradke, 2011) Links gephyrin to actin (Bausen et al., 2006; Giesemann et al., 2003)	
	N-WASP (Lim et al., 2008)	Promotes filopodia formation (Lim et al., 2008)	Neurite and spine development (Irie and Yamaguchi, 2004; Suetsugu et al., 2002; Wegner et al., 2008)	
	SH2B1 (Hong et al., 2014)	Promotes filopodia formation (Hong et al., 2014)	Dendrite formation and branching (Chen et al., 2015)	Developmental delay (Bachmann-Gagescu et al., 2010)
	Shank1 (Soltau et al., 2002)	Links Shank1 to Cdc42 and PSD-95 (Choi et al., 2005; Soltau et al., 2002)	Spine morphology and synaptic function (Sala et al., 2001)	ASD (Leblond et al., 2014; Sato et al., 2012) Schizophrenia (Lennertz et al., 2012)
	Shank3 (Bockmann et al., 2002)	Induces filopodia outgrowth in neuronal cell lines (Bockmann et al., 2002)	Dendritic spines (Roussignol et al., 2005)	ASD, Phelan-McDermid syndrome, schizophrenia, bipolar, hyperkinetic (Guilmatre et al., 2014; Han et al., 2013; Leblond et al., 2014)
	Spin90 (Teodorof et al., 2009)	Regulates Rac/Rho and actin filaments (Teodorof et al., 2009)	Dendritic spines (Cho et al., 2013; Kim et al., 2009b; Wagner et al., 2013)	
	Synaptopodin (Yanagida-Asanuma et al., 2007)	Inhibit Cdc42 and Mena binding to IRSp53 (Yanagida-Asanuma et al., 2007)	Spine apparatus and spine plasticity (Korkotian et al., 2014)	
	Tiam1 (Connolly et al., 2005)	Contributes to Rac signaling specificity (Connolly et al., 2005)	Spine development (Tolias et al., 2005; Tolias et al., 2007)	

Table 1 (*continued*)

Domain	Binding partner	Function of interaction	Partner's neuronal/synaptic function	Partner's association with brain disorders
	VASP (Disanza et al., 2013)	Promotes filopodia formation (Disanza et al., 2013)	Neuronal polarity (Drees and Gertler, 2008; Neukirchen and Bradke, 2011)	
	Wave-1 (Miki et al., 2000)	Links Rac and Wave (Miki et al., 1998; Miki et al., 2000)	Spines, synaptic plasticity, and memory (Hazai et al., 2013; Kim et al., 2006; Soderling et al., 2007)	
	Wave-2 (Miki et al., 2000)	Links Rac and Wave (Miki et al., 1998; Miki et al., 2000)	Likely dendritic spines (Choi et al., 2005; Ito et al., 2010; Lee et al., 2006; Soderling and Scott, 2006)	
PDZ-B	CIPP (Alpi et al., 2009; Barilari and Dente, 2010)	Form the CIPP-Cypin-IRSp53 complex (Barilari and Dente, 2010)	Synaptic membrane protein clustering (Kurschner et al., 1998)	ASD and Schizophrenia (Kenny et al., 2014)
	MALS/LIN-7 (Hori et al., 2003)	May translocate IRSp53 to cell −cell contacts (Hori et al., 2003)	Synapse development and function (Mizuno et al., 2015)	ASD (Mizuno et al., 2015)
	PSD-93 (Choi et al., 2005)	Synaptic localization of IRSp53 (Choi et al., 2005)	Postsynaptic protein scaffolding (Sheng and Kim, 2011)	ASD (Egger et al., 2014)
	PSD-95 (Choi et al., 2005; Soltau et al., 2004)	Synaptic localization of IRSp53 (Choi et al., 2005)	Postsynaptic protein scaffolding (Sheng and Kim, 2011)	ASD and William's syndrome (Feyder et al., 2010) Schizophrenia (Balan et al., 2013; Purcell et al., 2014)

domains of IRSp53, and protein kinase C-dependent phosphorylation of the IMD domain (Hori et al., 2005).

6. IRSp53 in dendritic spine development

Dendritic spines, protrusions in neurons with distinct membrane curvatures in sub-regions (i.e. head, wall, and neck), are well known for their actin-rich cytoskeleton (Cingolani and Goda, 2008; Harris and Weinberg, 2012; Penzes and Rafalovich, 2012; Sala and Segal, 2014; Tada and Sheng, 2006). Therefore, IRSp53, a regulator of membrane and actin dynamics, could be expected to play a role in the regulation of dendritic spine development and plasticity.

Dendritic spines contain a branched actin filament network in the head, and a network of branched and linear actin filaments in the spine neck and in dendritic filopodia (a possible precursor of dendritic spines), which are reported to contain tightly bundled actin filaments (Korobova and Svitkina, 2010). These authors suggest that an actin patch on the dendritic trunk elongates into a filopodium, and the tip expands into a mature spine head through the activity of the Arp2/3 complex, known to regulate dendritic spine structure and plasticity (Kim et al., 2013, 2015).

Providing a more dynamic view of spine actin regulation, a recent study using single protein tracking and super-resolution imaging has revealed an interesting nanoscale sub-spine segregation, where regulators of F-actin nucleation/branching such as IRSp53 and the WAVE complex are confined at the vicinity the PSD, whereas F-actin elongators such as VASP and formin-like protein-2 move outwards from the PSD with protrusion tips (Chazeau et al., 2014). This study also finds that Rac1 reaches the PSD through membrane free-diffusion and is immobilized at the PSD depending on its levels of activation, whereas the Arp2/3 complex reaches to the PSD through cytosolic free-diffusion. Moreover, conditions promoting spine enlargement such as constitutively active Rac1, or overexpressed Shank3, delocalize the WAVE complex from the PSD, and translocate the complex to the other parts of the spine to promote F-actin elongation throughout the spine.

Overexpression of IRSp53 in dissociated cultured hippocampal neurons increases spine density and size (Choi et al., 2005). Knockdown of IRSp53 decreases spine density, but not spine size (Choi et al., 2005). Similar to these results, excitatory synapses develop slowly in dissociated hippocampal neurons derived from *IRSp53*$^{-/-}$ mice (Sawallisch et al., 2009). *IRSp53*$^{-/-}$ mice display normal densities of excitatory synapses and dendritic spines in the hippocampus (Kim et al., 2009a; Sawallisch et al., 2009) but reduced excitatory synapse and spine densities in the medial prefrontal cortex (Chung et al., 2015). This indicates distinct influences of IRSp53 deletion on different brain regions. Phenotypes of *IRSp53*$^{-/-}$ mice are summarized in Table 2.

How might IRSp53 contribute to synaptogenesis? The CRIB-PR domain of IRSp53 can bind to activated Cdc42, which is tethered to the plasma membrane at sites of early synapses, promoting the membrane targeting and activation of IRSp53. This would allow the IMD domain of IRSp53 bind to and deform PI(4,5)P_2- and PI(3,4,5)P_3-rich plasma membranes to generate protrusive structures (Fig. 2). Concurrent with this, the IMD domain may interact with and bundle (or form a linear array of) actin filaments at sites of membrane deformation. This physical connection of the plasma membrane and actin filaments, which may also occur in mature synapses, would require a large amount of IRSp53 protein. Consistent with this possibility, IRSp53 is quite abundant in the PSD, where its levels are comparable to those of other scaffolding/adaptor proteins such as PSD-95, GKAP, Shank, and Homer (Cheng et al., 2006).

The SH3 domain of activated IRSp53 may also promote actin polymerization at sites of IRSp53 clustering in early and mature synapses in a neuronal activity- and Rac/Cdc42-dependent manner (Fig. 2). SH3 effectors such as Eps8, Ena/VASP, and mDia1, acting downstream of Cdc42, may drive the formation of linear actin filaments (Ahmed et al., 2010; Scita et al., 2008), while N-WASP and WAVE2, acting downstream of Rac, may promote branched actin filaments. In direct support of an important role of the SH3 domain in spine regulation, a mutant IRSp53 with a point mutation in the SH3 domain that abolishes effector binding, or a fragment of WAVE2 containing only the IRSp53-SH3-interacting proline-rich region, suppresses dendritic spine density in a dominant-negative manner when overexpressed in cultured hippocampal neurons (Choi et al., 2005).

In line with the critical roles of Cdc42 and Rac in IRSp53-dependent spine development mentioned above, activation of NMDARs and EphB receptors are known to stimulate Rac/Cdc42 through mechanisms including calcium/calmodulin-dependent kinases I/II (CaMKI/II) and a variety of GEFs such as Kalirin-7, Tiam1, GEFT, and α/βPix (ARHGEF6/7) (Penzes and Cahill, 2012;

Table 2
Electrophysiological and behavioral phenotypes of *IRSp53*$^{-/-}$ mice.

Phenotypes of *IRSp53*$^{-/-}$ mice		Changes	References
Electrophysiological phenotypes	AMPA-mEPSC in CA1	Normal	(Kim et al., 2009a)
	NMDA-mEPSC in CA1	Increased (ampl.)	(Kim et al., 2009a)
	PPF in DG *in vivo*	Increased	(Sawallisch et al., 2009)
	PPF in CA1	Increased	(Sawallisch et al., 2009)
	NMDA/AMPA ratio in CA1	Increased	(Kim et al., 2009a)
	LTP in DG *in vivo*	Increased	(Sawallisch et al., 2009)
	LTP in CA1	Increased	(Kim et al., 2009a; Sawallisch et al., 2009)
	LTD in CA1	Normal	(Kim et al., 2009a)
	mGluR-LTD in CA1	Normal	(Chung et al., 2015)
	LTD of NMDAR EPSCs in CA1	Impaired	(Chung et al., 2015)
	AMPA-mEPSC in mPFC	Decreased freq. & ampl.	(Chung et al., 2015)
	Firing rate in mPFC *in vivo*	Decreased	(Chung et al., 2015)
Behavioral phenotypes	Open field locomotion	Normal; Hyperactive	(Sawallisch et al., 2009); (Chung et al., 2015)
	Rotarod motor function	Normal	(Sawallisch et al., 2009)
	Contextual fear	Increased	(Sawallisch et al., 2009)
	Morris water maze memory	Impaired	(Kim et al., 2009a)
	Novel object recognition	Impaired	(Kim et al., 2009a)
	3-chamber social interaction	Decreased	(Chung et al., 2015)
	USV calls (to female)	Decreased	(Chung et al., 2015)

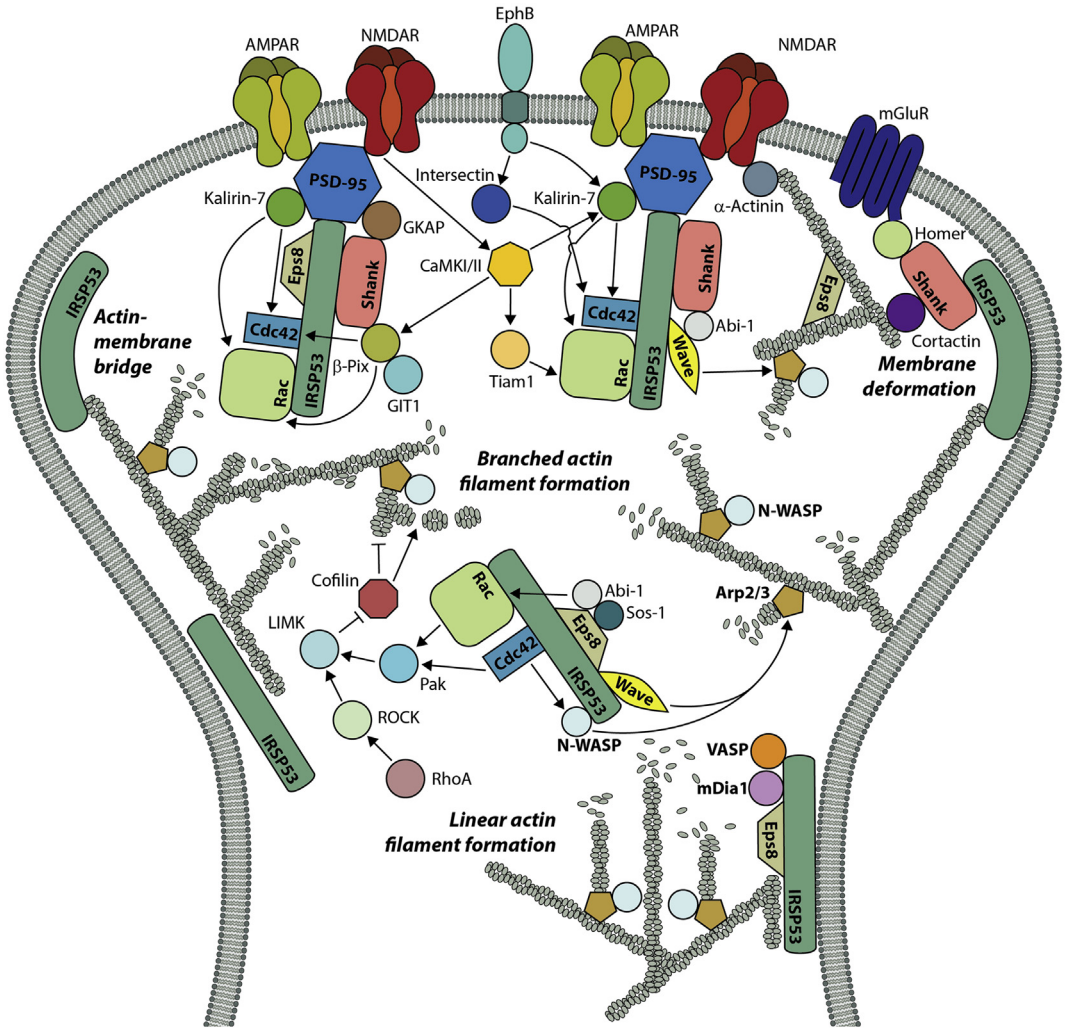

Fig. 2. A model for the proposed roles of IRSp53 in the development of dendritic spines. IRSp53 likely binds to and deforms the dendritic plasma membrane through the N-terminal IMD domain, producing a protrusive structure (*membrane deformation*). Once the activated (GTP-bound) form of Cdc42, which acts in the downstream of membrane proteins such as NMDARs, binds to and opens up IRSp53, IRSp53 will interact with and recruit diverse actin modulatory SH3 effectors. Effectors including Ena/VASP, mDia2, and Eps8 may promote linear actin filament formation (*linear actin filament formation*), likely driving the elongation and bundling of early dendritic protrusions. Others such as WAVE and N-WASP, acting in the downstream of Rac, may drive the formation of branched actin filaments in relatively mature dendritic spines by acting on the Arp2/3 complex (*branched actin filament formation*). IRSp53 is also thought to bridge the plasma membrane and actin filaments in dendritic spines through its IMD domain (*actin-membrane bridge*). The dual interaction of IRSp53 with the excitatory postsynaptic scaffolds PSD-95 and Shank may allow the formation of tighter and bigger structural and signaling complexes.

Penzes et al., 2008; Sala and Segal, 2014; Saneyoshi and Hayashi, 2012; Tolias et al., 2011). Conversely, Rac/Cdc42 activities can be suppressed by diverse GTPase activating proteins (GAPs), including intersectin, α1-chimaerin, Bcr/Abr, SRGAP2/3, and RhoGAP2, balancing the actions of Rac GEFs.

The C-terminal PDZ-binding motif of IRSp53 binds to the PDZ domains of the excitatory postsynaptic scaffolds PSD-95 and PSD-93/Chapsyn-110 (Choi et al., 2005; Soltau et al., 2004), interactions that appear to promote synaptic localization of IRSp53 (Choi et al., 2005; Hori et al., 2005) (Fig. 2). Conversely, IRSp53 may also recruit and stabilize PSD-95 at sites of early synaptic protrusions or mature dendritic spines where membrane deformation and actin polymerization/stabilization is occurring. IRSp53 may also form a ternary complex with PSD-95 and Shank (Soltau et al., 2004), leading to the formation of a bigger scaffolding/signaling complex in the PSD.

Given that the SH3 domain of IRSp53 can interact with diverse actin-regulatory proteins, it will be important to understand how various SH3 effectors cooperate with Rac/Cdc42 and IRSp53 to regulate the dynamics of branched and linear actin filaments during different stages of spine development and at multiple sub-spine domains. In addition, the types of SH3 effectors bound to IRSp53 and their phosphorylation states determine the direction and rate of actin filament growth during filopodia formation (Ahmed et al., 2010). It is therefore conceivable that synaptic receptors and associated signaling pathways acting upstream of IRSp53 may further coordinate IRSp53-dependent spine regulation.

7. IRSp53 in the regulation of excitatory synaptic transmission and plasticity

Given the importance of the actin cytoskeleton and its dynamics in the regulation of excitatory synaptic transmission and plasticity (Calabrese et al., 2006; Cingolani and Goda, 2008; Hotulainen and Hoogenraad, 2010; Oertner and Matus, 2005; Penzes and Rafalovich, 2012; Sala and Segal, 2014; Saneyoshi and Hayashi, 2012; Tada and Sheng, 2006), IRSp53 deletion in neurons could be expected to modify synaptic functions.

Indeed, overexpression of IRSp53, or a mutant form of IRSp53 that lacks the SH3 domain and is constitutively targeted to excitatory synapses, in cultured hippocampal neurons increases the amplitude of miniature excitatory postsynaptic currents (mEPSCs) (Hori et al., 2005), suggesting that IRSp53 positively regulates excitatory synaptic transmission. In contrast to these in vitro results, *IRSp53*$^{-/-}$ Schaffer collateral-CA1 pyramidal synapses in the hippocampus show normal amplitude and frequency of mEPSCs, input–output relationship of basal transmission, and paired pulse facilitation (PPF) (Kim et al., 2009a) (summarized in Table 2). Similar results were reported by another laboratory (Sawallisch et al., 2009), although this latter study did find an increase in PPF. *IRSp53*$^{-/-}$ synapses on dentate gyrus granule cells receiving inputs from the medial perforant pathway show unaltered basal transmission but increased PPF (Sawallisch et al., 2009). Collectively, these results suggest that AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor (AMPAR)-mediated synaptic transmission is largely normal in the hippocampus.

Intriguingly, however, NMDAR-mediated excitatory synaptic transmission is enhanced at *IRSp53*$^{-/-}$ SC-CA1 synapses, as measured by pharmacologically isolated NMDAR-dependent mEPSCs and evoked EPSCs (Kim et al., 2009a). In addition, long-term potentiation (LTP) is markedly enhanced, although long-term depression (LTD) is unaffected. These results suggest that NMDAR function is selectively enhanced at *IRSp53*$^{-/-}$ hippocampal synapses (Kim et al., 2009a; Sawallisch et al., 2009).

The *IRSp53*$^{-/-}$ mPFC region shows changes distinct from those in the hippocampus (Chung et al., 2015) (Table 2). The frequency and amplitude of mEPSCs are markedly reduced in *IRSp53*$^{-/-}$ prelimbic layer2/3 neurons, an effect that is paralleled by a decrease in excitatory synapse numbers, as shown by EM analysis. Unlike the case in the hippocampus, NMDAR function in the mPFC is unaltered, as measured by the NMDA/AMPA ratio. Therefore, the two *IRSp53*$^{-/-}$ brain regions display distinct electrophysiological changes: the hippocampus shows a decrease in NMDAR function with no change in excitatory synapse numbers, whereas the mPFC displays normal NMDAR function but a decrease in excitatory synapse numbers.

8. Mechanisms underlying NMDAR hyperactivity in *IRSp53*$^{-/-}$ hippocampal neurons

How might IRSp53 deletion lead to NMDAR hyperactivity in mice? The molecular abundance and functional properties of NMDARs at excitatory synapses are determined by a large number of factors, including subunit composition, protein modification, interacting proteins, and receptor trafficking into and out of synapses (Bard and Groc, 2011; Chen and Roche, 2007; Fan et al., 2014; Horak et al., 2014; Husi and Grant, 2001; Husi et al., 2000; Lau and Zukin, 2007; Newpher and Ehlers, 2008; Paoletti et al., 2013; Ryan et al., 2008; Sanz-Clemente et al., 2013). Therefore, comprehensively identifying all underlying mechanisms would be a daunting task, but it is possible that there may be increased influx, or reduced efflux, of NMDARs at *IRSp53*$^{-/-}$ synapses under basal conditions or during neuronal activity.

Previous studies have shown that actin filaments are important for synaptic localization and activity of NMDARs as well as AMPARs (Allison et al., 1998; Bosch and Hayashi, 2012; Furukawa et al., 1997; Rosenmund and Westbrook, 1993; Wyszynski et al., 1997). Consistent with this idea, actin filaments in *IRSp53*$^{-/-}$ hippocampal neurons are abnormally stable, exhibiting resistance to NMDA-induced dispersal (Chung et al., 2015). Given that the NMDA treatment induces a normal increase in cofilin activation/dephosphorylation in *IRSp53*$^{-/-}$ hippocampal neurons (Chung et al., 2015), it appears that actin filaments in these neurons became resistant to activated cofilin. In addition, *IRSp53*$^{-/-}$ SC-CA1 synapses show reduced LTD of NMDAR EPSCs (Chung et al., 2015), a form of synaptic LTD distinct from the better-understood LTD of AMPAR EPSCs in aspects including the underlying mechanisms; LTD of NMDAR EPSCs requires actin depolymerization, whereas LTD of AMPAR EPSCs requires calcineurin activation (Morishita et al., 2005; Selig et al., 1995). These results suggest the hypothesis that IRSp53 deletion leads to an abnormal stabilization of synaptic actin filaments, which may promote synaptic localization of NMDARs and suppress their activity-dependent removal (Fig. 3).

Given that IRSp53 interacts with a large number of proteins and that IRSp53 may regulate their stability, synaptic localization, and function, IRSp53-interacting proteins may contribute to the enhanced NMDAR function observed at *IRSp53*$^{-/-}$ hippocampal synapses. In line with this possibility, mice lacking Eps8, which directly interacts with IRSp53 (Funato et al., 2004), show abnormally stable actin filaments, reduced NMDA-induced cofilin activation/dephosphorylation, enhanced NMDAR function in cerebellar granule neurons, and increased ethanol resistance and consumption (Offenhauser et al., 2006). In addition, mice lacking WAVE-1, which interacts with IRSp53 (Miki et al., 2000) and regulates dendritic spines (Hazai et al., 2013; Kim et al., 2006; Soderling et al., 2007), display elevated NMDAR function and enhanced early and late LTP (Soderling et al., 2007). Dynamin-1, known to interact with IRSp53 (Chou et al., 2014), is required for NMDAR internalization induced by the dual binding of glutamate and glycine (Nong et al., 2003).

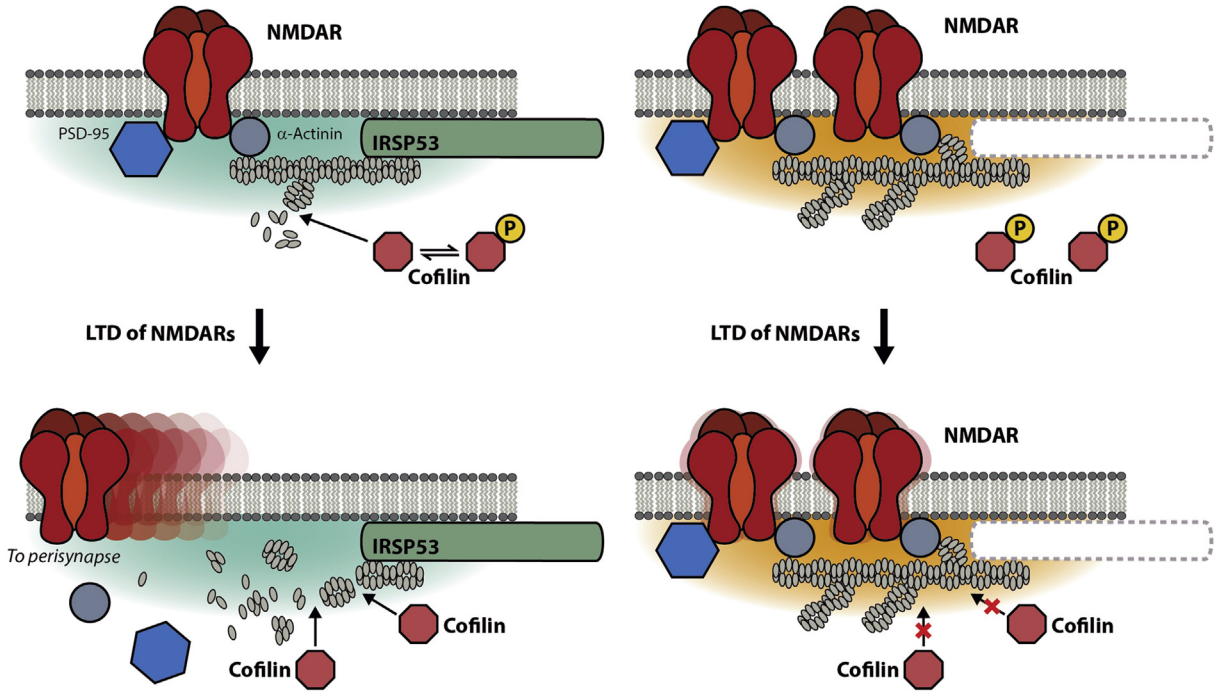

Fig. 3. A model for the proposed roles of abnormally stabilized actin filaments in anchoring of NMDARs at excitatory synapses. Under normal conditions, NMDARs are anchored at excitatory synapses through their interactions with PSD-95 family proteins and actin filaments through α-actinins. Stimuli inducing the LTD of NMDAR EPSCs cause actin depolymerization through the activation/dephosphorylation of cofilin (a negative actin regulator), leading to the removal of NMDARs from synapses through lateral diffusion. In the absence of IRSp53, synaptic actin filaments are abnormally stabilized through as of yet unclear mechanisms and become resistant to activated/dephosphorylated cofilin (dotted arrow), leading to enhanced synaptic retention of NMDARs under basal conditions and suppressed removal of NMDARs from synapses during LTD of NMDAR EPSCs.

9. Implications of IRSp53 in psychiatric disorders

Recent clinical studies have associated IRSp53/BAIAP2 with normal human brain functions (Luksys et al., 2014) and several psychiatric disorders, including ASDs (Celestino-Soper et al., 2011; Levy et al., 2011; Toma et al., 2011), schizophrenia (Fromer et al., 2014; Purcell et al., 2014), and ADHD (Liu et al., 2013; Ribases et al., 2009). A common SNP (single-nucleotide polymorphism) variant located in the *BAIAP2* gene in healthy individuals has been associated with emotional regulation of human memory strength (Luksys et al., 2014). In this study, modulation of verbal memory strength by negative information was associated with SNP genotype, activity of the parahippocampal cortex, and *BAIAP2* mRNAs levels.

In individuals with ASDs and schizophrenia, several SNPs were associated with disease susceptibilities (Ribases et al., 2009; Toma et al., 2011). In addition, de novo copy number variations (deletions) that eliminate the entire *IRSp53* gene were identified in individuals with ASD (Celestino-Soper et al., 2011; Levy et al., 2011). De novo missense and nonsense mutations in the *IRSp53* gene that lead to an F486L aa substitution in a region following the WW domain and truncation of the protein in the IMD domain, respectively, have also been identified in schizophrenic patients (Fromer et al., 2014; Purcell et al., 2014). Additional details are summarized in Table 3.

10. Behavioral phenotypes of *IRSp53*$^{-/-}$ mice

Behavioral phenotypes of *IRSp53*$^{-/-}$ mice have been characterized (Chung et al., 2015; Kim et al., 2009a; Sawallisch et al., 2009). *IRSp53*$^{-/-}$ mice show impaired social interaction, as determined by three-chamber and direct social interaction tests (Chung et al., 2015) (Table 2). In addition, ultrasonic vocalization in the presence of a stranger female is reduced in male *IRSp53*$^{-/-}$ mice. However, *IRSp53*$^{-/-}$ mice do not show enhanced repetitive behaviors, such as grooming and digging.

IRSp53$^{-/-}$ mice have been reported to display hyperactivity in both novel and familiar environments (Chung et al., 2015), though another study reported largely normal locomotor activity of *IRSp53*$^{-/-}$ mice in a novel environment (Sawallisch et al., 2009). Given that the two studies use mice produced from the same ES cell line (XG757; BayGenomics), the discrepancy might stem from their different genetic backgrounds: C57BL/6J (Chung et al., 2015) and 129P2/C57BL/6 hybrid (Sawallisch et al., 2009).

In terms of cognitive function, *IRSp53*$^{-/-}$ mice show impairments in Morris water maze spatial learning (Kim et al., 2009a), and novel object recognition memory (Kim et al., 2009a). Intriguingly, *IRSp53*$^{-/-}$ mice show increased contextual fear conditioning 24 h after the training (Sawallisch et al., 2009).

These results collectively suggest that *IRSp53*$^{-/-}$ mice exhibit social and cognitive deficits and hyperactivity, which may have features in common with the symptoms of IRSp53-associated psychiatric disorders (e.g., ASDs, schizophrenia, and ADHD). Although these behavioral phenotypes tend to support the validity of the *IRSp53*$^{-/-}$ mouse model, the predictive value of this model depends on a demonstration of pharmacological reversal of the phenotypes.

11. Reversal of abnormal phenotypes in *IRSp53*$^{-/-}$ mice by NMDAR suppression

Starting from the premise that abnormal behaviors of IRSp53$^{-/-}$ mice are caused by elevated NMDAR function, a logical intervention is to attempt to normalize these behaviors by pharmacological suppression of NMDAR function. Memantine, an uncompetitive antagonist of NMDARs, is used clinically to improve cognitive functions in brain disorders, including Alzheimer's disease, and is

Table 3
Associations of IRSp53 with psychiatric disorders.

Disorders	Genetic variations	Locations of mutations	References
ASD	SNP (rs11657991)	Intron 2	(Toma et al., 2011)
	De novo CNV (deletion)	Not applicable	(Celestino-Soper et al., 2011)
	De novo CNV (deletion)	Not applicable	(Levy et al., 2011)
Schizophrenia	Missense (F486L)	Exon 12 (After WW domain)	(Fromer et al., 2014)
	Codon deletion (CCCT → C)	3′-UTR (chr17:79089626–79089629)	
	Nonsense (G → T)	Exon 2 (IMD domain; chr17:79027528)	(Purcell et al., 2014)
ADHD	SNP (rs8079626, rs11657991, rs7503597, rs7210438)	Introns 1, 2, 3, 5	(Ribases et al., 2009)
	SNP (rs4969239, rs3934492, rs4969385)	Introns 1, 3, 6	(Liu et al., 2013)

known to be well tolerated likely due to its moderate affinity and voltage-dependent channel-blocking property (Parsons et al., 2013; Thomas and Grossberg, 2009).

Consistent with the NMDAR hyperfunction hypothesis, acute memantine treatment (10 mg/kg) 30 min before behavioral testing significantly improves the social interaction of *IRSp53*$^{-/-}$ mice in the three-chamber test, without affecting that of wild-type mice (Chung et al., 2015). In addition, memantine normalizes the impaired novel object recognition in *IRSp53*$^{-/-}$ mice, suggesting an effect on cognitive functions. However, memantine has no effect on the hyperactivity in these animals.

Indirect suppression of NMDAR function in *IRSp53*$^{-/-}$ mice by MPEP (2-methyl-6-(phenylethynyl)pyridine), a negative allosteric modulator of metabotropic glutamate receptor 5 (mGluR5), a receptor type that acts synergistically with NMDARs (Alagarsamy et al., 1999; Jia et al., 1998; Kotecha and MacDonald, 2003; Lu et al., 1999; O'Connor et al., 1994), rescues social interaction deficits in *IRSp53*$^{-/-}$ mice. This provides further evidence for an association between NMDAR hyperfunction and the social deficits in *IRSp53*$^{-/-}$ mice.

How could the *IRSp53*$^{-/-}$ mPFC, which shows normal NMDAR function, be involved in the memantine-dependent rescue of social deficits in these animals? *IRSp53*$^{-/-}$ neurons in the mPFC display reduced excitatory neuronal firing with unaltered inhibitory neuronal firing (Chung et al., 2015). In addition, this phenotype is rescued by acute memantine treatment. This links normalization of neuronal firing in the *IRSp53*$^{-/-}$ mPFC with the memantine-dependent NMDAR suppression and rescue of social and cognitive deficits in *IRSp53*$^{-/-}$ mice, although further mechanistic details remain to be elucidated.

12. Therapeutic potential of NMDAR suppression for social and cognitive deficits associated with ASDs, schizophrenia, and ADHD

Results from IRSp53 studies suggest the therapeutic potential of NMDAR suppression in alleviating social and cognitive deficits associated with ASDs, schizophrenia, and ADHD. The therapeutic potential of memantine in the treatment of psychiatric disorders has gained credence, but remains controversial (Canitano, 2014; Doyle and McDougle, 2012; Hosenbocus and Chahal, 2013; Rossignol and Frye, 2014; Sani et al., 2012; Shim and Nadeem, 2014). As such, the following issues, which are in principle testable in model animals, need to be clarified.

First of all, it is unclear where in the brain the abnormally enhanced NMDAR function resides and how it is associated with the observed social and cognitive impairments. In the case of IRSp53, the protein is detected in different regions of the brain (cortex, hippocampus, striatum, and cerebellum), cell types (spiny excitatory and inhibitory neurons), and lateral locations within the PSD (higher in the center vs. evenly distributed) (Burette et al., 2014), suggesting that IRSp53 may have distinct functions at different spatial locations.

Second, the list of animals that show enhanced NMDAR function and social and cognitive deficits that are improved by NMDAR-suppressing medications needs to be expanded. For instance, rats prenatally exposed to valproic acid (an antiepileptic agent with teratogenic activity), which show ASD-like phenotypes (social and repetitive behavior deficits), display enhanced NMDAR levels and LTP in the cortex (Rinaldi et al., 2007), indicative of enhanced NMDAR function. In addition, social defects and repetitive behaviors in mice prenatally exposed to valproic acid are suppressed by NMDAR inhibition through acute treatment with memantine or MPEP treatment (Kang and Kim, 2015; Kim et al., 2014).

This new possibility—NMDAR suppression to alleviate social and cognitive deficits in psychiatric disorders—needs to be reconciled with other emerging and established factors contributing to ASDs, schizophrenia, and ADHD such as excitation-inhibition balance (Bourgeron, 2009; Gao and Penzes, 2015; Rubenstein, 2010; Rubenstein and Merzenich, 2003; Yizhar et al., 2011), hyper-dopamine/hypo-glutamate (Coyle, 2012; Coyle et al., 2012), and hypo-dopamine mechanisms (Chang et al., 2014; Levy, 2014), respectively.

Memantine acts on other types of receptors in addition to NMDARs, functioning as antagonists at serotonin (5-HT_3) and nicotinic acetylcholine receptors, and as an agonist at dopamine (D_2) receptors (McKeage, 2009, 2010). The potential involvement of these activities in the observed rescue effects in *IRSp53*$^{-/-}$ mice should be clarified, although the similar rescue produced by the suppression of mGluR5, which acts synergistically with NMDARs, supports the NMDAR hyperfunction hypothesis (Chung et al., 2015).

In addition to enhanced NMDAR function, reduced NMDAR function has also been associated with ASD-like phenotypes in animal models of ASDs (Blundell et al., 2010; Lee et al., 2015; Won et al., 2012). Therefore, how deviation of NMDAR function in either direction—enhancement or suppression—is associated with similar social deficits should be clarified.

Lastly, clinical trials of memantine for ASD treatment have yielded significant improvements in 8 out of 9 studies (Rossignol and Frye, 2014); higher-quality and larger-scale clinical studies should follow. Despite these encouraging results, memantine has been found to both improve and worsen irritability, suggesting that memantine may work for a specific subgroup of patients. The possible bidirectional deviation of NMDAR function in the social deficits noted above might explain the clinical data.

13. Conclusion

This review summarized the suggested roles of IRSp53 in the regulation of synaptic actin/membranes, spine development, and synaptic function and plasticity. In addition, we described the role of NMDAR suppression in the reversal of the social and cognitive deficits observed in *IRSp53*$^{-/-}$ mice, which may help us understand IRSp53-related and other actin/NMDAR-related psychiatric disorders.

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